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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,786	04/11/2001	David J. Diller	1073.060A	4635

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EXAMINER

LY, CHEYNE D

ART UNIT PAPER NUMBER

1631

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/832,786	Applicant(s) DILLER ET AL.	
	Examiner Cheyne D Ly	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 September 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>9/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicants' arguments filed September 22, 2003 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. This rejection is maintained with respect to claims 1-15, as recited in the previous office action mailed May 21, 2003.

Response to Applicant's Argument

5. Applicant argues that the term complementarity is well known in the art by citing that the term has been used specifically in the Rarey et al. (1996) reference. Applicant's argument has been fully considered and found to be unpersuasive due to Rarey et al. specifically states that complementarity is determined by steric effects of the protein-ligand complex. The usage of the term complementarity causes the claims to be vague and indefinite in the instant claims because Applicant does not state the criteria being used to define the complementarity of a target to a ligand.

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6. Specific to claims 1 and 6, line 2; claims 2, 7, and 12, line 2; and claim 11, line 3, the term “complementarity” causes the claims to be vague and indefinite. The term “complementarity” is unclear because Applicant does not state the criteria being used to define the complementarity of a target to a ligand. Is a target complementary to a ligand in regard to its conformation or molecular bonding properties? Applicant can resolve this issue by particularly pointing out the criteria that is used to determine that a target is complementary. Clarification of the metes and bounds of the instant claims is required. Claims 3-5, 8-10, and 13-15 are rejected for being directly or indirectly dependent from claim 1, 2, 6, 7, 11, or 12.

LACK OF ENABLEMENT UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method, system and program storage device for assessing a combinatorial library wherein the ligands of the said library are complementary to either plasmepsin or cathepsin, does not reasonably provide enablement for a method, system and program storage device for assessing a combinatorial library wherein the ligands of the said library are complementary to any target. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

9. This rejection is maintained with respect to claims 1-15, as recited in the previous office action mailed May 21, 2003.

Response to Applicant's Argument

10. Applicant argues the claimed method is fully enabled with respect to the scope of the claims because the instant invention has been demonstrated with 103 structures that are well established in the Protein Data Bank (PDB). Applicant's argument has been fully considered and found to be unpersuasive as discussed below.

11. Applicant points to pages 14-38 to argue that the instant method is enabled for at least the 103 structures. This is confusing because the same disclosure (pages 14-38), referred to by the instant specification, defines the state of the art (docking procedure) at the time of the invention, identifies problems with the said docking procedure, and discusses how the instant invention addresses said problems. Is Applicant's argument directed to the docking procedure of Jones et al. (page 15, [0044]) which has been faulted by the instant specification or the instant invention?

12. It is re-iterated that the factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The

Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

13. It is acknowledged that the applicant has disclosed information to enable one skilled in the art to use specific crystallographic observations directed to plasmepsin or cathepsin for assessing a combinatorial library (Page 38, Table 7). However, a method, system or program storage device that relies on data from an unpredictable art such as protein crystallization would require clear and precise guidance for one skilled in the art to reliably use the said method. It is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). Further, as recently as November 1, 2002, Science published a New Focus article depicting the current state of the art for protein crystallization that supports the unpredictability of the art. In essence, protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized. Therefore, researchers continue to have trouble generating sufficient protein required for the crystallization process (New Focus, Science, 2002). Accordingly, it would be unpredictable for one skilled in the art to use the method, system or program storage device of this instant application to assess combinatorial libraries based on the observed crystallographic data of any other receptor beyond the ones of the instant application. In light of the difficulty of the protein crystallization process, it is, therefore, unreasonable to expect one skilled in the art to use the method, system or program storage device that relies on observed crystallographic data produced from an unpredictable

process to predictably assess combinatorial libraries using crystallographic data directed to any other target receptor without undue experimentation.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1, 2, 5, 6, 7, 10-12, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al. (1994) taken with Rarey et al. (1996).

17. This rejection is maintained with respect to claims 1, 2, 5, 6, 7, 10-12, and 15, as recited in the previous office action mailed May 21, 2003.

Response to Applicant's Argument

18. Applicant argues that the cited references either alone or in combination (Ho et al., Rarey et al., DeLisi et al., and Aldenderfer et al.) are "silent regarding docking compounds of

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a combinatorial library, and assessing whether the library as a whole is likely to contain a significant number of compounds that bind to a particular target. Further, the said references do not disclose comparing position of the common core of each compound as docked in the binding site with the position of the common core of the other compounds in the library in the binding site. Applicant's arguments have been fully considered and found to be unpersuasive as discussed below.

19. It is noted that Applicant directs said argument above specifically to references Ho et al. and Rarey et al.; therefore, the instant response is directed to the references Ho et al. and Rarey et al. However, the instant response has been extended to the disclosure of Ho et al. and Rarey et al. in combination with DeLisi et al., and Aldenderfer et al. in the following 35 USC §103 rejections.

20. Consistent with the combinatorial library of the instant invention (page 5, [0021]), Ho et al. discloses libraries having thousands of compounds that has potential bind to the target and are thus termed "ligands" and combining the first and second library a cycloX2_dbase is generated. The cycloX2_dbase database consists of structures having two rings (common core) and lined by short chains (page 216, column 16-33). In generating said database, a user can specify hydrophobic anchoring segments or flexible chains containing hydrogen bonding elements are needed (variable constituents) (page 215, column 2, lines 48-54). The method and a system consisting of four programs for searching for complementary components in a chemical library and the search produces 63 structures that matched at least four query requirements (an assessment of the above combinatorial library) (page 216, column 1, lines

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35-41). Therefore, Rarey et al. in combination with Ho et al. disclose the limitations of the instant claims 1-15.

21. It is re-iterated Ho et al. discloses a method and a system consisting of four programs for searching for complementary components in a chemical library and the search produces 63 structures that matched at least four query requirements (page 216, column 1, lines 35-41), as in instant claims 1, 6, and 11. Foundation approximates the fit of each component with the active site. SPLICE compensates for atomic motion of the receptor atoms by decreasing the van der Waals radii to ensure each structure stably fits with the active site. Ligands identified above are processed and clipped off until the structure is satisfactory (page 216, lines 8-48). Further, Splice screens the components in the active site and determines pairs of matched structures (page 217, lines 35-38) and images of novel ligands generated by SPLICE after matching analysis (Figure 7), as in instant claims 5, 10, and 15.

22. However, Ho et al. does not disclose the limitations of determining an rms deviation or forming clusters.

23. Rarey et al. discloses a method for placing molecular fragments into the active site of a receptor based on rms deviations for a receptor (Abstract etc.). The result of the method of Rarey et al. is a ranking based on minimum rms deviations (Table 5), as in instant claims 1, 2, 6, 7, 11 and 12.

24. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the concept emphasized by Ho et al. for a method and a system consisting of four programs for searching for complementary components in a chemical

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library and improve on it by using the method and computer of Rarey et al. to optimize the drug design process by ranking ligands based on rms deviations (page 41, lines 7-9).

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use a method and a system to search for complementary components in a chemical library as taught by Ho et al. and rank ligands based on rms deviations as taught by Rarey et al.

25. Claims 1-3, 5-8, 10-13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al. (1994) taken with Rarey et al. (1996) in view of DeLisi et al. (1996).

26. Ho et al. discloses a method and a system to search for complementary components in a chemical library and Rarey et al. discloses a method for ranking ligands based on rms deviations as cited above, as in instant claims 1, 2, 5, 6, 7, 10-12, and 15.

27. This rejection is maintained with respect to claims 1-3, 5-8, 10-13, and 15, as recited in the previous office action mailed May 21, 2003.

28. However, Ho et al. and Rarey et al. do not disclose the limitations of determining an rms by using a grid.

29. DeLisi et al. discloses a method for computing the conformation and location that a protein fragment will obtain in binding to the active site by using of a grid for determining rms deviations (column 12, lines 26-64), as in claims 3, 8, and 13.

30. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the concept emphasized by Ho et al. and Rarey et al. for a method and a system to search for complementary components in a chemical library and rank ligands based

on rms deviations; and improve on their methods by using a grid to determine the rms deviations as taught by DeLisi et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use a method and a system to search for complementary components in a chemical library as taught by Ho et al., rank ligands based on rms deviations as taught by Rarey et al. and determine the rms deviations as taught by DeLisi et al.

31. Claims 1, 2, 4, 5, 6, 7, 9-12, 14, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al. (1994) taken with Rarey et al. (1996) in view of Aldenderfer et al. (1984).

32. Ho et al. discloses a method and a system to search for complementary components in a chemical library and Rarey et al. discloses a method for ranking ligands based on rms deviations as cited above, as in instant claims 1, 2, 5, 6, 7, 10-12, and 15.

33. However, Ho et al. and Rarey et al. do not disclose the limitations of forming clusters using a single linkage-clustering algorithm.

34. Aldenderfer et al. discloses a review of hierarchical clustering methods including single-linkage clustering algorithm (page 39-40), as in claims 4, 9, and 14.

35. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the concept emphasized by Ho et al. and Rarey et al. for a method and a system to search for complementary components in a chemical library and rank ligands based on rms deviations; and improve on their methods by using a type of hierarchical clustering algorithm such as a single-linkage clustering algorithm. Therefore, it would have been

obvious to one having ordinary skill in the art at the time of the invention was made to use a method and a system to search for complementary components in a chemical library as taught by Ho et al., rank ligands based rms deviations as taught by Rarey et al. and cluster using a single-linkage clustering algorithm.

CONCLUSION

36. NO CLAIM IS ALLOWED.

37. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

38. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

39. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 872-9306.


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40. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (703) 308-3880. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

41. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

42. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
11/20/03


JOHN H. MARCHESI
11/20/03